Madison, Wis. September 18, 1952

Dear Luca:

What with the paperwork waiting for me, and new students coming in for the new university session, I was delayed a few days in studying the "final" version of our JGM paper. I must admit that it does read better now even than the American version. In order to avoid confusion I think that all corrections in proof should be cleared through you. If some changes are possible, I would like to discuss the following. In a few places, I notice sentences that are absolutely identical with those in the American version. I think these should be either paraphrased or omitted. The page references are to the "final" ms. (I am amused at the editor's having p 3 caught the "thorough" search for F+ to F- mutants. I pulled the same sort of error in another ms. where I refer to E. coli and Salmonella as distant and close relatives in the same paragraph. It just shows how meaningless such fortifying adjectives really are!) p5 line 13-14 I would delete the sentence (especially as I did not in practise aerate for this purpose) and put aeration (by rolling) in the previous line. line 21: what does the editor say about loopfuls/loopsful? FOWLER agrees with you. p 6. lines 18ff. I agree this should be omitted with a reference to LCL 53. p 7 lines 12-13. This seems to suggest that the inhibitor destroys the agent. Better: certain inhibitors (...) of enzymes which etc. p8 line2 I am waiting to have a proper physical analysis done of collison theory for bacterial kinetics, but it is questionable in my mind whether or not stirring influences the chance of collision. Unless you are confident about the physical theory, it might be better to write , may influence the success of contact..., instead of , probably more important, the chance of contact .... p9 line20 Strictly speaking, transduce means approximately transfer, so that the F+ agent is transduced to an F- cell, not an F- cell transduced to F+. I have violated this usage in the same way myself, but am uncomfortable about it and would welcome your suggestions. Originally, I intended "transduction" as a term with its own meaning, but it gradually came to be transduced to its present special use. Perhaps one could say transinduced, (but this would need to be specially defined) for the alteration of a cell via transduction. Would it be possible to paraphrase lines 21-29? p13 line 21. F+ is correct. It might be better to omit this paragraph or insert the information elsewhere. p15 line 8 "prototrophs" is not the right word. Perhaps "zygotes" here, and insert "prototrophic" before heterozygotes. line 12 In American usage, one might quibble about "crossing-over" which to us means the genetic observation of recombination of linked markers, for which the physical basis is chiasmata. Perhaps delete physical, or leave it alone. p18 last PAR. The argument appears to be circular (as one defines F+ in terms of fertility) until one reaches the discussion of Hfr. If one can still make so drastic a change (and I very hesitantly suggest this), it might be better to reorganize the paragraph, beginning with the notion that Hfr forms an apparent exception to the rule that an F+ agent is essential. However, etc. to the distinction between the F agent and the F+ state. p. 21 line 2 ff. There is some confusion in the references to hypothesis 1 and 2 and possibilities 1,2,3. You seem to give the least weight to my favorite: Hyp 1 Poss 3, which is perhaps fortunate as indicating at least some divergence in our otherwise monotonous agreement of views. The occasional appearance of loci (e.g. Lac) in homozygous condition in the persistent diploids is the main basis of my current preference , but I certainly would not insist on the acceptance of it, just as you tolerate my adherence to it in the American version. Galley proof has just been corrected for the latter, with no noticeable changes from the agreed ms.

Of course I hope to continue our collaboration! I would still make the request that we can pursue these studies without undue pressure by at least discouraging the distribution of Hfr to other workers, for the time being. I would find it psychologically very difficult to continue working at it if I knew anyone else were on the same job, unless I could enjoy the very close communication with him as we have, I think, succeeded in establishing. As I wrote earlier, I have been looking for microscopically visible tags to distinguish the parent cells. Tri-phenyltetrazolium works very well, but I do not have a satisfactory second tag. For a while, I though a blue tz derivative would do, but this turned out to be unusually toxic. We have not yet seen mating per se (having had the same observational difficulties you mention) but have isolated single cells from previously mixed cultures, some of which proved to be zygotes. The records of them show them to be essentially

typical in appearance, perhaps larger than the norm. I have already mentioned observations of what appear to be droplets of some exudate as seen in heavily stained (Giemsa) fixed slides, especially in Hfr, and the occurrence of cells that looked asif they might be stuck together by the exudate (once or twice in living material like this:  It was especially striking when one cell was stuck to the substratum, and the other revolved about the point of attachment. Perhaps some of the flagella were entangled, and I cannot be sure of the significance of the observations.

Dr. T.C.Nelson has come to work with me on these problems. We have not yet set out our immediate program, but one of the items is to look for conditions that permit zygote-initiation without growth, which might allow the accumulation of actively mating attached-pairs. His earlier work on the kinet. of recombination with Nfr was based on this possibility, but it may have been an agglutination which may or may not be an artefact. He will probably also try to develop the use of M-T-L-F+ as a technique for studying the kinetics of F+ transduction, but we await your comments on this. I myself will probably continue the cytology, and also concentrate on the genetics of Hfr. I have some definite indications that Hfr is on the same eliminated segment as Mal, but this is not yet proven. We will probably also try to make a quantitative assessment of mating efficiency in various F+/F- and F+/F+ combinations, by way of testing the relative potency hypothesis.

In any event, we will keep you fully informed, and look for the same from yourself.

Sincerely,

Joshua

Joshua Lederberg

P.S. I have read your ms. (from Szybalski) on polygenic control of drug-resistance, and enjoyed it very much. Your paper for the Chemical Microbiology Center (just seen in the W.H.O. Bulletin) was also a beautiful piece of writing. Card wrote to you! I hope you have an ample supply of reprints for the latter.